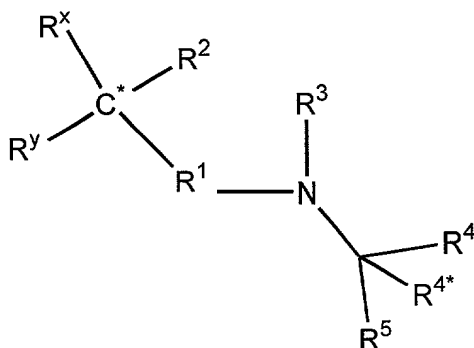


APPENDIX A: HIGHLIGHTED LEAD CLAIM 43

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43. A compound of the following formula:



or a pharmaceutically acceptable salt thereof,

wherein:

- (1) C^* is a substituted carbon;
- (2) R^2 (a) is hydrogen, (C1-C6) alkyl, (C1-C6) alkoxy, cyano, (C2-C7) alkanoyl, aminocarbonyl, (C1-C6) alkylaminocarbonyl, or dialkylaminocarbonyl wherein each alkyl is independently C1 to C6, (b) comprises (where R^1 is not aminoethylene, $-O-R^8$ or $-S-R^{8*}$) hydroxy, fluoro, chloro, bromo or (C2-C7) alkanoyloxy, (c) forms a double bond with an adjacent carbon or nitrogen from one of either R^1 , R^{xb} or R^{yb} , (d) is R^{2a} linked by R^{2b} to C^* , or (e) is ethylene forming a third bridging structure as set forth in (2ⁱⁱⁱ)(b)(i);
- (2ⁱ) R^x is R^{xa} linked by R^{xb} to C^* ;
- (2ⁱⁱ) R^y is R^{ya} linked by R^{yb} to C^* ;
- (2ⁱⁱⁱ) R^{xa} and R^{ya} , are independently Ar, which is phenyl or naphthyl, heteroaryl, or or a 5 to 7-membered non-aromatic ring having from 0 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and R^{2a} , when present, is Ar, and wherein:
 - (a) heteroaryl comprises thienyl, furanyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, or one of the foregoing fused to phenyl, or methylenedioxyphenyl,

APPENDIX A: HIGHLIGHTED LEAD CLAIM 43

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- (b) each of R^{xa} and RY^a can be independently substituted with one of R^q , R^rO - or R^sS -, wherein each of R^q , R^r and R^s are independently Ar, heteroaryl, adamantyl, or a 5 to 7-membered non-aromatic ring having from 0 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and
- (c) R^{xa} , RY^a , R^{2a} , R^q , R^r and R^s can be substituted or additionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, bromo, nitro, hydroxy, cyano, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C12) alkyl, (C2-C12) alkenyl, amino, (C1-C6) alkylamino, dialkylamino wherein each alkyl of dialkylamino is independently C1 to C6, (C1-C6) alkoxy, (C2-C7) alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7) alkyloxycarbonyl, aminocarbonyl that can be substituted for hydrogen with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, or amidino wherein the amidino can be independently substituted with up to three (C1-C6) alkyl groups, wherein:
- (i.) the substitutions of R^{xa} and RY^a can be combined to form a second bridge between R^{xa} and RY^a comprising (1) methylene or ethylene, which methylene or ethylene can be substituted by an R^2 when R^2 is ethylene to form the third bridging structure, or (2) $-CH=CH-$, or (3) sulfur, or (4) oxygen, or wherein R^{xa} and RY^a can be directly linked by a single bond,
- (d) wherein at least one of R^{xa} , RY^a , R^q , R^r or R^s is heteroaryl, or a second bridge between R^{xa} and RY^a comprises sulfur or oxygen as set forth below, or Ar substituted with a methylenedioxy;
- (2iv) R^{xb} and R^{2b} are independently a single bond or (C1-C2) alkylene;

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(2^v) R^{y_b} is a single bond, oxy, (C1-C2) alkylene, ethenylene or -CH= (where the double bond is with C^{*}), thio, methyleneoxy or methylenethio, or either -N(R⁶) or -CH₂-N(R^{6*})-, wherein R⁶ and R^{6*} are hydrogen or (C1-C6) alkyl;

(3) R¹ comprises: a straight-chained (C2-C3) aliphatic group; =N-O-(ethylene), wherein the unmatched double bond is linked to C^{*}; -O-R⁸ or -S-R^{8*} wherein R⁸ or R^{8*} is a ethylene or ethenylene and O or S is bonded to C^{*}; aminoethylene where the amino is bonded to C^{*}:

wherein R¹ can be substituted with up to one hydroxy, up to one (C1-C6) alkoxy or up to one (C2-C7) alkanoyloxy, with up to two independent (C1-C6) alkyl, with up to one oxo, up to one (C1-C6) alkylidene, with the proviso that the hydroxy, alkoxy, alkanoyloxy or oxo substituents are not bonded to a carbon that is bonded to a nitrogen or oxygen;

wherein if R¹ contributes a heteroatom linked to C^{*}, then R^{y_b} does not contribute a heteroatom linked to C^{*}; and

wherein the alkyl or alkylidene substituents of R¹ can be linked to form a 3 to 7-membered non-aromatic ring;

(4) R³ (a) is hydrogen, (C1-C6) alkyl, or phenyl or phenylalkyl wherein the alkyl is C1 to C6 and the phenyl or phenyl of phenylalkyl can be substituted with the same substituents defined above for the phenyl of R^{x_a}, (b) is -R¹²C(R^{xx})(R^{yy})(R¹¹), wherein R¹² is bonded to N, R^{xx} is independently the same as R^x, R^{yy} is independently the same as R^y, R¹¹ is independently the same as R² and R¹² is independently the same as R¹;

(5) R⁴ and R^{4*} are independently hydrogen or (C1-C6) alkyl, or one of R⁴ and R^{4*} can be (C1-C6) hydroxyalkyl; and

(6) R⁵ is (CO)NR¹³R¹⁴, (CO)OR¹⁵, (CO)SR¹⁶, (SO₂)NR¹⁷R¹⁸, (PO)(OR¹⁹)(OR²⁰), (CR²²)(OR²³)(OR²⁴), CN or tetrazol-5-yl, wherein (a) R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ R¹⁹

APPENDIX A: HIGHLIGHTED LEAD CLAIM 43

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and R²⁰ are independently hydrogen, (C1-C8) alkyl which can include a (C3-C8) cycloalkyl, wherein the carbon linked to the oxygen of R¹⁵ or the sulfur of R¹⁶ has no more than secondary branching, (C2-C6) hydroxyalkyl, aminoalkyl where the alkyl is C2 to C6 and the amino can be substituted with up to two independent (C1-C6) alkyls, Ar-alkyl wherein the alkyl is C1-C6, or Ar, and (b) R²² is hydrogen or OR²⁵ and R²³, R²⁴ and R²⁵ are independently (C1-C6) alkyl, phenyl, benzyl or acetyl or, the alkyls of R²³ and R²⁴ can be combined to include 1,3-dioxolane or 1,3-dioxane:

wherein the phenyl or naphthyl groups of R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²², R²³ or R²⁴ can be substituted with substituents selected from the group consisting of fluoro, chloro, bromo, nitro, cyano, hydroxy, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C6) alkyl, (C2-C6) alkenyl, (C1-C6) alkylamine, dialkylamine wherein each alkyl is independently C1 to C6, amino, (C1-C6) alkoxy, (C2-C7) alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7) alkyloxycarbonyl, aminocarbonyl that can be N-substituted with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, or amidino that can substituted with up to three (C1-C6) alkyl;

wherein R¹³ and R¹⁴ together with the attached nitrogen can form a 5 to 7-membered ring.

44. The compound of claim 43, wherein at least one of R^{xa}, R^{ya}, R^q, R^r and R^s is thienyl or furanyl.

45. The compound of claim 43, wherein at least one of R^{xa} and R^{ya} is thienyl or furanyl.

APPENDIX A: HIGHLIGHTED LEAD CLAIM 43

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47. The compound of claim 46, wherein at least one of R^{xa} , R^{ya} , R^q , R^r and R^s is substituted with fluoro, trifluoromethyl, trifluoromethoxy, nitro, cyano, or (C3-C8) alkyl.

53. The compound of claim 51, wherein R^5 is (CO)OR¹⁵ and R^{15} is (C2-C6) alkyl, (C2-C4) hydroxyalkyl, phenyl, phenylalkyl wherein the alkyl is C1-C3, or aminoalkyl where the alkyl is C2-C6 and the amino can be substituted with up to two independent (C1-C3) alkyls, wherein the phenyl or the phenyl of phenylalkyl can be substituted.

54. The compound of claim 51, wherein R^5 is (CO)OR¹⁵ and R^{15} is hydrogen.

62. **The compound of claim 43, wherein R_3 is hydrogen, (C1-C6) alkyl, or phenyl or phenylalkyl wherein the alkyl is C1 to C6 and the phenyl or phenyl of phenylalkyl can be substituted with the same substituents defined above for the phenyl of R^{xa} .**

66. The compound of claim 43 wherein:

- (1) R^2 is hydrogen,
- (2) R^{xa} and R^{ya} are phenyl, **thienyl or furanyl, and can be substituted,**
- (3) R^{xb} is a single bond and R^{yb} is a single bond or oxy, and
- (4) R^5 is (CO)NR¹³R¹⁴ or (CO)OR¹⁵, wherein R^{13} , R^{14} , and R^{15} are independently hydrogen; (C1-C8) alkyl which can include a (C3-C8) cycloalkyl, wherein the carbon linked to the oxygen of OR¹⁵ has no more than secondary branching; (C2-C6) hydroxyalkyl or aminoalkyl where the alkyl is C2 to C6 and the amino can be substituted with up to two independent (C1-C6) alkyl or phenylalkyl, wherein the alkyl is C1-C6 and the phenyl can be substituted with substituents selected from the group consisting of fluoro, chloro, bromo, nitro, cyano, hydroxy, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C6) alkyl, (C2-C6) alkenyl, (C1-C6) alkylamine, dialkylamine wherein each alkyl is independently C1 to C6, amino, (C1-C6) alkoxy, (C2-C7)

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alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7)

alkyloxycarbonyl, aminocarbonyl that can be N-substituted with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, amidino that can substituted with up to three (C1-C6) alkyl.

67. The compound of claim 66, wherein R² forms a double bond with an adjacent carbon from R¹.

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Application papers not suitable for publication

SN 09-757-011 Mail Date 01-09-01

- ☐ Non-English Specification
- ☒ Specification contains drawing(s) on page(s) _____ or table(s) 62-63
- ☐ Landscape orientation of text ☐ Specification ☐ Claims ☐ Abstract
- ☐ Handwritten ☐ Specification ☐ Claims ☐ Abstract
- ☐ More than one column ☐ Specification ☐ Claims ☐ Abstract
- ☐ Improper line spacing ☐ Specification ☐ Claims ☐ Abstract
- ☐ Claims not on separate page(s)
- ☐ Abstract not on separate page(s)
- ☐ Improper paper size -- Must be either A4 (21 cm x 29.7 cm) or 8-1/2"x 11"
- ☐ Specification page(s) _____ ☐ Abstract
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- ☐ Excessive text, drawing(s) _____
- ☐ Photographs capable of illustration, drawing(s) _____

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- 3,3,3-tris(4-chlorophenyl)propanol *p*-toluenesulfonate [prepared by LiAlH_4 reduction of 3,3,3-tris(4-chloropropionic acid) (Aldrich) followed by tosylation of the formed alcohol];
- 17) 3-(2-naphthyl)-3-phenyl)propanol *p*-toluenesulfonate [prepared by Horner-Emmons reaction of the sodium ylide of triethyl phosphonoacetate with 2-benzoylnaphthalene (Aldrich) followed by
- 5 catalytic hydrogenation of the intermediate α,β -unsaturated ester, LiAlH_4 reduction and tosylation of the formed alcohol]; 18) 3,3,3-triphenylpropanol *p*-toluenesulfonate [prepared by LiAlH_4 reduction of 3,3,3-triphenylpropionic acid (Aldrich) followed by tosylation of the formed alcohol];
- 19) 3-(4-phenylphenyl)-3-phenylpropanol *p*-toluenesulfonate [prepared by Horner-Emmons reaction of the sodium ylide of triethyl phosphonoacetate with 4-benzoylbiphenyl (Aldrich)
- 10 followed by catalytic hydrogenation of the intermediate α,β -unsaturated ester, LiAlH_4 reduction and tosylation of the formed alcohol]; 20) 1,2-diphenylbutan-1,4-diol *p*-toluenesulfonate [prepared by C-alkylation of deoxybenzoin (Aldrich) with ethyl bromoacetate (Aldrich) followed by LiAlH_4 reduction of the intermediate β -ketoester and tosylation of the formed diol]; 21)
- 3-phenyl-3-(4-trifluoromethylphenyl)propanol *p*-toluenesulfonate prepared by Horner-Emmons
- 15 reaction of the sodium ylide of triethyl phosphonoacetate with 4-(trifluoromethyl)benzophenone (Aldrich) followed by catalytic hydrogenation of the intermediate α,β -unsaturated ester, LiAlH_4 reduction and tosylation of the formed alcohol]; 22) 3-chloro-1-(4-*tert*-butylphenoxy)-1-(4-fluorophenyl)propane [prepared analogously to the method of U.S. Pat. 5,281,624 by reduction of 3-chloro-4'-fluoropropiophenone (Aldrich) with 1.0 M borane-
- 20 tetrahydrofuran complex ("BTC", Aldrich) followed by Mitsunobu reaction (diethyl azodicarboxylate ("DEAD"), Ph_3P , see Example 8C, Step 1) of the resulting alcohol with 4-*tert*-butylphenol (Aldrich)]; 23) 3-chloro-1-(2-methyl-5-pyridyloxy)-1-phenylpropane [prepared by reduction of 3-chloropropiophenone (Aldrich) with 1.0 M BTC followed by Mitsunobu reaction (DEAD, Ph_3P) of the resulting alcohol with 5-hydroxy-2-methylpyridine (Aldrich)]; 24)
- 25 3-chloro-1-(4-phenylphenoxy)-1-(4-fluorophenyl)propane [prepared by reduction of 3-chloro-4'-fluoropropiophenone with 1.0 M BTC followed by Mitsunobu reaction (DEAD, Ph_3P) of the resulting alcohol with 4-phenylphenol (Aldrich)]; 25) 3-chloro-1-(4-*tert*-octylphenoxy)-1-phenylpropane [prepared by reduction of 3-chloropropiophenone with 1.0 M BTC followed by Mitsunobu reaction (DEAD, Ph_3P) of the resulting alcohol with 4-*tert*-butylphenol]; 26)
- 30 (*R*)-(+)-3-chloro-1-(4-phenylphenoxy)-1-phenylpropane [prepared by Mitsunobu reaction (DEAD, Ph_3P) of (*R*)-(+)-3-chloro-1-phenyl-1-propanol (Aldrich) with 4-phenylphenol (Aldrich)](see, e.g., U.S. Pat. 5,068,432) (Reaction illustrated in Fig. 3, Reaction 27)]; Compound A61 was prepared